PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 60815	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/12056	International filing date *(day/month/year)* 02.10.2003	Priority date *(day/month/year)* 02.10.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/50		
Applicant THERAPTOSIS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the International application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.04.2004	18.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Tuynman, A Telephone No. +31 70 340-3741

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12056

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-28 as originally filed

Claims, Numbers

1-12 as originally filed

Drawings, Sheets

1/12-12/12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☒ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 10-12

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 10-12

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-9 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-9
	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item IV
Lack of unity of invention

The present application (PA) relates to the provision of modulators of mitochondrial function.

The technical feature of method claim 1 resides in the step of observing the effect of candidate compounds on mitochondrial functioning in a screening assay. Neither the same nor a corresponding special technical feature (Rule 13.2 PCT) is present in any of the compounds claimed in claims 10-12. No manufacturing relationship exists between the screening method and the claimed compounds. Further the screening method is not a method of using the claimed compounds. Therefore, there is no single general concept that links the method to the claimed compounds.

Thus unity of invention is lacking a priori between the method claims (claims 1-9) and the compound claims (claims 10-12).

As to the compounds disclosed in the present application, sufficiency of disclosure (Article 5 PCT) can only be found for the peptides mentioned on page 6-9 (SEQ ID NO 1-57). The only teaching as to the structure required for a compound to act as a modulator of mitochondrial functioning is given on page 7 of the description, lines 1-14.

The problem to be solved by the present application can be considered as the provision of modulators of mitochondrial functioning. The single general concept which can be identified a priori as linking the claimed compounds and which forms a solution to the above mentioned problem is a compound fulfilling the structural requirements mentioned on page 7 of the description, lines 1-14.

However, Pfeiffer et al., Journal of Biochemistry, Vol. 270, No. 9, pp. 4923-4932 (hereinafter referred to as D1, relevant passages: abstract, Table I) discloses such compounds. In the light of D1, the above identified single general concept is not novel and inventive and can thus not be the single general inventive concept as required by Rule 13.1 PCT. The present application is therefore considered not to fulfil the requirement of unity as laid down in Rule 13.1 PCT.

Therefore the groups of inventions are split up as follows:
1) methods for screening modulators of mitochondrial function (claims 1-9 fully).
2) synthetic peptides that induce cell death of various cell types, group 1 on page 8 of

the description and structural analogs (SEQ ID No 2-4,8,9,12-18,36-41; claims 10-12 partially)
3) synthetic peptides that induce cell death of adenocarcinoma cell lines; group 2 on page 9 of the description and structural analogs (SEQ ID NO 10,11,24-35,42-53; claims 10-12 (partially))
4) synthetic peptides that induce cell death of HUVECs; group 3 on page 9 of the description and structural analogs (SEQ ID NO 5,20-23,54-57; claims 10-12 (partially)).
5) synthetic peptide according to SEQ ID No 1 as modulator of mitochondrial function 6) synthetic peptide according to SEQ ID No 6 as modulator of mitochondrial function 7) synthetic peptide according to SEQ ID No 7 as modulator of mitochondrial function 8) synthetic peptide according to SEQ ID No 19 as modulator of mitochondrial function

The invention first mentioned in the claims (involving methods for screening modulators of mitochondrial function) has been searched. No additional search fees have been paid. Therefore the present opinion on novelty, inventive step and industrial applicability shall be restricted to group 1 of inventions i.e. claims 1-9.

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: PFEIFFER DOUGLAS R ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 270, no. 9, 1995, pages 4923-4932.
D2: MINAMIKAWA TETSUHIRO ET AL: EXPERIMENTAL CELL RESEARCH, vol. 246, no. 1, 10 January 1999 (1999-01-10), pages 26-37.
D3: MINAMIKAWA T ET AL: JOURNAL OF CELL SCIENCE. ENGLAND JUL 1999, vol. 112 (Pt 14), July 1999 (1999-07), pages 2419-2430.

The document D4 was not cited in the international search report. A copy of the document is appended hereto.

D4: MACOUILLARD-POULLETIER DE GANNES F ET AL: CYTOMETRY, 1998, vol.33, pages 333-339.

1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of independent claims 1 is not new in the sense of Article 33(2) PCT.

The document D4 discloses (the references in parentheses applying to this document): D4 (abstract) discloses a method for screening modulators of mitochondrial function comprising adding a compound (acetyl-ceramide) to be tested in a purified, isolated mitochondria preparation and simultaneously using fluorimetric analysis of mitochondrial morphology, and especially real-time fluorimetric analysis, combining analysis of morphometric parameters (SSC/FSC parameters) with analysis of membrane integrity by dye fluorescence (via the fluorescent probe DiOC6).

2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9 does not involve an inventive step in the sense of Article 33(3) PCT.

2.1 Dependent claims 2-9 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to inventive step, the reasons being as follows: The incorporation of the features of claims 2-9 into independent claim 1 is either obvious from D1-D4 or fall within the knowledge and ability of a person skilled in the art.

3 The subject matter of claims 1-9 is industrially applicable in the sense of Article 33(4) PCT.

4 Present claim 1 is not clear in the sense of Article 6 PCT.

4.1 It is unclear whether the features "SSC/FSC parameters" are optional features or not, since these features have been written between brackets. In the present analysis these features have been considered as optional features. They can be rendered limiting by omitting the brackets. It should furthermore be clarified that FSC and SSC mean forward scatter and side scatter, respectively, since the terms FSC and SSC are not generally accepted terms in the prior art.

4.2 The applicant is informed that due to the term "especially" in claim 1, the feature of "real-time fluorimetric analysis" is also considered to be an optional feature and therefore does not limit the claim.